

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/165, 9/14, 9/20		A1	(11) International Publication Number: WO 98/47499 (43) International Publication Date: 29 October 1998 (29.10.98)
(21) International Application Number: PCT/JP98/01769			(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CZ, EE, GE, GW, HU, ID, IL, IS, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 17 April 1998 (17.04.98)			
(30) Priority Data: 9/117463 22 April 1997 (22.04.97) JP			
(71) Applicant (<i>for all designated States except US</i>): NIPPON KAYAKU KABUSHIKI KAISHA [JP/JP]; 11-2, Fujimi 1-chome, Chiyoda-ku, Tokyo 102-8172 (JP).			
(72) Inventors; and			Published
(75) Inventors/Applicants (<i>for US only</i>): HAMADA, Akinobu [JP/JP]; 6-8-22, Kamiochiai, Yono-shi, Saitama 338-0001 (JP). YAHIRO, Tomio [JP/JP]; 6-11-15, Kamiochiai, Yono-shi, Saitama 338-0001 (JP).			With international search report.
(74) Agents: ASAMURA, Kiyoshi et al.; New Ohtemachi Building, Room 331, 2-1, Ohtemachi 2-chome, Chiyoda-ku, Tokyo 100-0004 (JP).			
(54) Title: FLUTAMIDE PREPARATIONS AND METHOD FOR MANUFACTURING THE SAME			
(57) Abstract			
A pharmaceutical flutamide preparation prepared from a co-pulverized mixture of flutamide with an excipient and a solubilizer exhibits an improved dissolution property of the active ingredient, and thus provides a higher bioavailability of flutamide.			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

DESCRIPTION

FLUTAMIDE PREPARATIONS AND METHOD FOR
MANUFACTURING THE SAME

TECHNICAL FIELD

The present invention relates to a pharmaceutical preparation comprising flutamide (hereinafter often referred to as "flutamide preparation") as an active ingredient. The present invention also relates to a method for manufacturing the flutamide preparation.

BACKGROUND ART

Flutamide is a generic name for 4'-nitro-3'-trifluoromethylisobutyranilide approved by the United States Adopted Names. Pharmaceutical preparations comprising flutamide as an active ingredient have currently been used for the treatment of prostatic carcinoma. Specific formulations of such pharmaceutical preparations of flutamide are described in, for example, USP 4,474,813.

Flutamide is hydrophobic drug and it is generally considered that flutamide would readily be agglomerated due to the inherent re-agglomerating nature of flutamide and result in a reduction in the dissolution rate of flutamide in the pharmaceutical preparation.

SUMMARY OF THE INVENTION

The present invention provides a novel flutamide pharmaceutical preparation which exhibits the pharmacological effect of flutamide comparable and 5 equivalent to conventional flutamide preparations even though the content of flutamide in the preparation is reduced.

The present invention also provides a method for manufacturing the flutamide pharmaceutical solid 10 preparation exhibiting improvable or comparable bioavailability even with such a reduced content of flutamide.

As a result of extensive studies to achieve the foregoing objects, the present inventors have 15 accomplished the present invention. Thus, the present invention is concerned with the flutamide pharmaceutical preparations and methods for manufacturing the preparations.

Thus the present invention provides pharmaceutical solid preparation comprising flutamide as an 20 active ingredient and having a dissolution property that, when determined according to a paddle method, at least 50% of the flutamide dissolves out from the preparation 30 minutes after initiation of a test 25 according to the paddle method.

The pharmaceutical solid preparation comprises flutamide as an active ingredient together with a pharmaceutically acceptable additive which is preferably

crystalline cellulose.

In a preferred aspect of the present invention, the pharmaceutical solid preparation is obtainable by formulating a co-pulverized mixture of flutamide with 5 an excipient and/or a solubilizer into a pharmaceutical solid preparation.

In a preferred aspect of the pharmaceutical solid preparation of the said excipient is crystalline cellulose, and said solubilizer is sodium lauryl 10 sulfate.

The present invention also provides a method for manufacturing a flutamide pharmaceutical preparation which comprises the steps of:

subjecting flutamide and an excipient and/or a 15 solubilizer to co-pulverization using a comminuting machine; and

formulating the resulting co-pulverized mixture into a pharmaceutical solid preparation.

In a preferred aspect of the method of the 20 present invention, said solubilizer has been previously milled using a ball mill, then to the resulting milled powders are added flutamide and the excipient followed by co-pulverization by a comminuting machine and formulation into a pharmaceutical solid preparation.

25 In another preferred aspect of the method of the present invention, flutamide, the excipient and the solubilizer have been previously mixed with each other,

then the resulting mixture is subjected to copulverization by a surface modifying machine followed by formulation into a pharmaceutical solid preparation.

In another preferred aspect of the method of
5 the present invention, said excipient is crystalline cellulose, and said solubilizer is sodium lauryl sulfate.

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 shows the results from the dissolution
10 test for the pharmaceutical preparation of the present invention and Odyne® Tablet for comparison.

Fig. 2 shows the results from absorption test
for the pharmaceutical preparation of the present
invention and Odyne Tablet for comparison when
15 administered into dogs.

Fig. 3 shows the results from absorption test
for the pharmaceutical preparation of the present
invention and Odyne tablet for comparison when
administered into human.

20 DETAILED DESCRIPTION OF THE INVENTION

In the present invention, the pharmaceutical solid preparation is in the form of, for example, and not by way of limitation, tablets, capsules, powders, granules, etc. Particularly, the preparation is
25 preferably in the form of tablets.

The solid preparation of the present invention

comprises flutamide as an active ingredient and has a dissolution property that, when determined according to a paddle method, at least 50% of the flutamide dissolves out from the preparation 30 minutes after initiation of
5 a test according to the paddle method.

Preferably at least 60%, more preferably at least 70%, most preferably at least 85% of the flutamide dissolves out from the solid preparation of the present invention 30 minutes after initiation of the test
10 according to the paddle method. In particular, where at least 90% of the flutamide dissolves the solid pharmaceutical preparation of the present invention is most effective as a drug.

The paddle method used herein is, more specifically, Dissolution Test 2 in accordance with the Japanese Pharmacopoeia, 13th revision. The Dissolution Test 2 of the Japanese Pharmacopoeia, 13th revision is specifically defined as follows;

a device used is equipped with a container of
20 1000 ml volume with a hemispherical bottom, a paddle, a thermostat water bath and a motor;

a rotor of the paddle is designed to have a lower bottom of 42.0 mm with a height of 19.0 \pm 0.5 mm by cutting a disk of 41.5 mm in a radius and 4.0 \pm 1.0
25 mm in a thickness with a parallel chord, and the upper left and right ends of the rotor have a radius of 1.2 mm;

the rotor with a rotating shaft of 9.4 ± 1.0 mm in a width penetrates through the center of the rotating shaft in such a manner that the lower bottom is at a surface level with the lower end of the rotating 5 shaft on the same surface, to fix vertically with the rotating shaft;

the upper end of the rotating shaft of the paddle is mounted to a supporting shaft designed to rotate together with the motor;

10 the paddle is dipped in a test solution (1% SDS solution, 900 ml) charged in the container which is previously adjusted to a temperature of $37 \pm 0.5^\circ\text{C}$ and rotated at 50 rpm, during which rotation, the rotating shaft is fixed so as to keep a distance of at least $25 \pm$ 15 2 mm between the lower end of the paddle and the inner bottom of the container; and,

the test is conducted by rotating the paddle at a predetermined position immediately after sinking a specimen (220 mg of the specimen in the case of powders) 20 at the center of the inner bottom of the container, collecting an eluate 30 minutes after and calculating a dissolution rate of the active ingredients from the solid preparation.

In the present invention, the solid prepara-
25 tion may contain the pharmaceutically acceptable additive. Examples of the additive may be an excipient including disintegrators or binders, a solubilizer, a lubricant and other additives that may be conventionally

used in pharmaceutical solid preparations.

In the present invention, excipients conventionally used for solid pharmaceutical preparations may be used without any particular limitation, so long as
5 the excipients can provide the solid pharmaceutical preparation having the dissolution property as defined above. The excipient may also be used in combination of one or more of the other excipient. Typical examples of the excipient include sugars such as glucose, fructose,
10 lactose, anhydrous lactose, sucrose, maltose, mannitol, xylitol, sorbitol, etc.; starch and derivatives thereof such as corn starch, partly pregelatinized starch, potato starch, wheat starch, etc., cellulose derivatives thereof such as crystalline cellulose.

15 The solid pharmaceutical preparation of the present invention may contain a solubilizer and other additives such as disintegrators, lubricants, binders, etc. that are conventionally used for solid pharmaceutical preparations. Specific examples of the
20 solubilizer are various types of surface active agents such as sodium lauryl sulfate (SDS), sorbitan fatty acid esters, polysorbate, lecithin, etc. In the present invention, it is particularly preferred to use sodium lauryl sulfate. Specific examples of disintegrators
25 include cellulose and derivatives thereof such as crystalline cellulose, low degree substitution hydroxypropyl cellulose, carboxymethyl cellulose, calcium carboxymethyl cellulose; starch and derivatives thereof

such as croscarmellose, hydroxypropyl starch, carmellose, partly pregelatinized starch, etc. Specific examples of binders are crystalline cellulose, methyl cellulose, hydroxypropyl cellulose (HPC), hydroxy-
5 propylmethyl cellulose, sodium carboxymethyl cellulose, partly pregelatinized starch, polyvinylpyrrolidone, polyvinyl alcohol, etc. Specific examples of lubricants include magnesium stearate, stearic acid, talc, silica, light anhydrous silicic acid, etc.

10 In the present invention, the content of flutamide in the solid pharmaceutical preparation is preferably in the range of about 5 to about 80 wt%, more preferably about 20 to about 40 wt%. The content of pharmaceutically acceptable additives in the solid
15 pharmaceutical preparation is preferably in the range of about 20 to about 95 wt%, more preferably about 60 to about 80 wt%.

In a preferred embodiment of the present invention, the pharmaceutical preparation comprises
20 flutamide of about 15 to about 50 wt%, preferably about 20 to about 40 wt% based on the total weight of the preparation, and the balance of pharmaceutically acceptable additives. The pharmaceutical additives are preferably in the range of about 50 to about 85 wt%,
25 more preferably about 60 to about 80 wt% based on the total weight of the preparation. The solubilizer may not always be necessary but optionally and preferably used in the range of about 0.01 to about 50 wt%, more

preferably about 0.1 to about 5 wt% based on the total weight of the preparation.

Generally, flutamide may be administered into a human in a unit dose of 30 to 300 mg.

5 In the meantime, even if the preparation of the present invention is reduced in the content of flutamide to 30 to 80% of that of the conventional flutamide preparations, the preparation of the present invention can provide a blood level of flutamide equivalent or comparable to that of conventional preparations, when administered into a human. Thus, in the preparation according to the present invention, a unit dose of flutamide may be reduced to 30 to 200 mg, preferably 30 to 100 mg, more preferably 50 to 90 mg.

10 In a specific embodiment of the present invention, the following components may be exemplified as a unit dosage form for the flutamide preparation.

	<u>Components</u>	<u>mg</u>
	Flutamide	50 - 180
20	Crystalline cellulose	40 - 240
	SDS	0.1 - 20
	Anhydrous lactose	30 - 140
	Partly pregelatinized starch	10 - 80
	HPC	1 - 20
25	Carmellose	5 - 80
	Lubricant	0.1 - 10

The flutamide preparation of the present invention may be manufactured according to a method which comprises subjecting flutamide together with an excipient or a solubilizer, preferably an excipient and 5 a solubilizer, to co-pulverization and then optionally to granulation into a pharmaceutical preparation.

Alternatively, the flutamide preparation of the invention may also be manufactured according to a method which comprises blending flutamide with an excipient and 10 a solubilizer, and subjecting the resulting blend to a heat treatment for thermal granulation into a pharmaceutical preparation. In a preferred embodiment of the present invention, the co-pulverized mixture is mixed with additives necessary for the pharmaceutical preparation, and the resulting mixture is subjected to 15 granulation in a conventional manner. For the granulation, wet granulation, dry granulation and thermal granulation are generally available, but wet granulation is particularly preferred in the present invention.

20 For the co-pulverization, employed are a ball mill, a speed mill, a pin mill, a hammer mill, a surface modifying machine (HYBRIDIZER, trademark, made by Nara Machinery Co., Ltd., Tokyo) and the like. In particular, it is preferred to use a ball mill and a surface modifying machine. When flutamide together with an 25 excipient are co-pulverized using a ball mill (speed of rotation: 60 rpm, 30-60 minutes), it is preferred that a solubilizer has been previously grinded with the ball

mill (speed of rotation: 60 rpm, 3-10 minutes).

Likewise, when flutamide together with an excipient are co-pulverized using a surface modifying machine, it is preferred that flutamide, an excipient and a solubilizer
5 have been previously blended in the machine.

In the co-pulverized mixture, the excipient may be contained in the range of approximately 0.3 to 2.0 parts by weight, preferably 0.6 to 1.2 parts by weight, and the solubilizer is in the range of approximately 10 0.005 to 0.5 part by weight, preferably 0.01 to 0.3 part by weight, based on 1 part by weight of flutamide. When the co-pulverized mixture is prepared in the present invention, the excipient and the solubilizers as illustrated hereinabove are available.
15 In a preferred embodiment of the present invention, crystalline cellulose and mannitol are employed as the excipient and SDS as the solubilizer, respectively.

A preferred example of the components for the co-pulverized mixture is as follows:

20	<u>Components</u>	<u>part by weight</u>
	Flutamide	60
	Crystalline cellulose	48
	SDS	1.8

When the mixture having the above components before co-pulverized is subjected to a powder size distribution test as defined in the General Rule for Pharmaceutical Preparations of the Japanese

- 5 Pharmacopoeia, only 80% or less of the mixture passes through a 48 mesh sieve. However, the mixture after co-pulverized exhibits an improvement that an agglomerating property of flutamide per se has been improved and that the fluidity of flutamide has been also improved. Thus,
10 at least 90% of the co-pulverized mixture, preferably at least 95%, more preferably 97.5% or more, passes through a 48 mesh sieve.

The powder size distribution test as stated above is defined in the Japanese Pharmacopoeia, and the
15 details of the procedure are as follows.

After 10.0 g of a specimen is accurately weighed, the specimen is put on a sieve of 48 mesh. The sieve is covered at the upper aperture. While shaking horizontally for 3 minutes, the sieve is tapped to
20 screen the powders. The screening are then weighed. The inner diameter of the sieve used for this test is set to 75 mm.

Since flutamide is hydrophobic, it is generally considered that flutamide would readily be
25 agglomerated due to the re-agglomerating nature of flutamide itself, which would result in reduction in the dissolution rate of flutamide in the pharmaceutical

preparation. The present invention using the co-pulverized mixture can surprisingly provide the pharmaceutical preparation markedly improved in the dissolution rate of flutamide.

5 The pharmaceutical preparation of the present invention is orally administered into a human. Flutamide is generally administered at a dose of 125 mg three times per day (Odyne Tablet, 1 tablet) in Japan, and in other countries, flutamide is administered at a
10 dose of 250 mg three times per day. For example, in the United States, two EULEXIN capsules, each containing 125 mg of flutamide, are orally administered three times per day. That is, a daily dose is 375 mg in Japan, and 750 mg in other countries. In the flutamide preparation of
15 the present invention, a unit dose can be reduced to 30 to 80% of the dose for conventional preparations. Even in the such a reduced dose of flutamide, the flutamide preparation of the present invention exhibits a blood level comparable to that of conventional preparations,
20 when administered into a human. Thus, it can be expected that in a less dose, the flutamide preparation of the present invention exhibits the pharmacological and clinical effects equivalent and comparable to that of the conventional pharmaceutical preparations.

25 The pharmaceutical preparation of the present invention has the dissolution property that flutamide can rapidly dissolve out from the preparation. Therefore, even though the content of flutamide in a unit

dosage is less than conventional flutamide preparations, the blood level of flutamide comparable to that of the conventional preparations can be obtained, when administered into a human. Moreover, differences in the 5 blood level between individuals administered can be minimized according to the flutamide preparation of the present invention.

The present invention is specifically explained with reference to the following examples.
10 Those examples are presented by way of illustration and not by way of limitation.

Example 1

1.8 g of SDS was milled in a ball mill (rotation: 60 rpm, 5 minutes). To the milled SDS were 15 added 48 g of crystalline cellulose and 60 g of flutamide. The resulting blend was subjected to co-pulverization (rotation: 60 rpm, 40 minutes). To the resulting co-pulverized powders were added 56.65 g of anhydrous lactose, 24.3 g of partly pregelatinized starch, 5 g of HPC and 23.25 g of carmellose. The 20 resulting mixture was then subjected to wet granulation followed by size reduction. After mixing further with 1 g of magnesium stearate, the resulting mixture was compression-molded with a tabletting machine to give 25 tablets of the present invention having components as mentioned below, each tablet weighing 220 mg in total.

	<u>Tablet formulation</u>	<u>Components (mg)</u>
	Flutamide	60
	Crystalline cellulose	48
	SDS	1.8
5	Anhydrous lactose	56.65
	Partly pregelatinized starch	24.3
	HPC	5
	Carmellose	23.25
	Magnesium stearate	1
10		

Example 2

2.4 g of SDS has milled in a ball mill (rotation: 60 rpm, 5 minutes). To the milled SDS were added 64 g of crystalline cellulose and 80 g of flutamide, and the resulting blend was co-pulverized (rotation: 60 rpm, 40 minutes). To the resulting powders were added 45.05 g of anhydrous lactose, 19.3 g of partly pregelatinized starch, 5 g of HPC and 23.25 g of carmellose. The resulting mixture was then subjected to wet granulation followed by size reduction. After mixing further with 1 g of magnesium stearate, the resulting mixture was compression-molded with a tabletting machine to give tablets of the present invention having components as mentioned below, each tablet weighing 240 mg in total.

	<u>Tablet formulation</u>	<u>Components (mg)</u>
	Flutamide	80
	Crystalline cellulose	64
	SDS	2.4
5	Anhydrous lactose	45.05
	Partly pregelatinized starch	19.3
	HPC	5
	Carmellose	23.25
	Magnesium stearate	1

10

Example 3

1.8 g of SDS, 48 g of crystalline cellulose and 60 g of flutamide were blended followed by copulverization (rotation; 4800 rpm, 1 minute) with a 15 surface modifying machine (HYBRIDIZER, trademark, Nara Machinery Co., Ltd., Tokyo). To the resulting powders were added 56.65 g of anhydrous lactose, 24.3 g of partly pregelatinized starch, 5 g of HPC and 23.25 g of carmellose. The resulting mixture was subjected to wet 20 granulation followed by size reduction. After mixing further with 1 g of magnesium stearate, the resulting mixture was compression-molded with a tabletting machine to give tablets of the present invention having components as mentioned below, each tablet weighing 220 25 mg in total.

	<u>Tablet formulation</u>	<u>Components (mg)</u>
	Flutamide	60
	Crystalline cellulose	48
	SDS	1.8
5	Anhydrous lactose	56.65
	Partly pregelatinized starch	24.3
	HPC	5
	Carmellose	23.25
	Magnesium stearate	1

10

Example 4

12.5 g of SDS was milled in a ball mill (rotation: 60 rpm, 5 minutes). To the milled SDS were added 50 g of crystalline cellulose and 62.5 g of flutamide, and the resulting blend was co-pulverized (rotation: 60 rpm, 40 minutes). To the resulting co-pulverized powders were added 56.5 g of anhydrous lactose, 24.25 g of partly pregelatinized starch, 5 g of HPC and 23.25 g of carmellose. The resulting mixture was then subjected to wet granulation followed by size reduction. After mixing further with 1 g of magnesium stearate, the resulting mixture was compression-molded with a tabletting machine to give tablets of the present invention having components as mentioned below, each tablet weighing 235 mg in total.

	<u>Tablet formulation</u>	<u>Components (mg)</u>
	Flutamide	62.5
	Crystalline cellulose	50
	SDS	12.5
5	Anhydrous lactose	56.5
	Partly pregelatinized starch	24.25
	HPC	5
	Carmellose	23.25
	Magnesium stearate	1
10		

Example 5

62.5 g of crystalline cellulose and 62.5 g of flutamide were blended in a ball mill followed by co-pulverization (rotation: 60 rpm, 40 minutes). To the 15 resulting co-pulverized powders were added 56.5 g of anhydrous lactose, 24.25 g of partly pregelatinized starch, 5 g of HPC and 23.25 g of carmellose. The resulting mixture was then subjected to wet granulation followed by size reduction. After mixing further with 1 20 g of magnesium stearate, the resulting mixture was compression-molded with a tabletting machine to give tablets of the present invention having components as mentioned below, each tablet weighing 235 mg in total.

	<u>Tablet formulation</u>	<u>Components (mg)</u>
	Flutamide	62.5
	Crystalline cellulose	62.5
	Anhydrous lactose	56.5
5	Partly pregelatinized starch	24.25
	HPC	5
	Carmellose	23.25
	Magnesium stearate	1

10 Example 6

6.25 g of SDS was milled in a ball mill (rotation: 60 rpm, 5 minutes). To the milled SDS were added 56.25 g of crystalline cellulose and 62.5 g of flutamide, and resulting the blend was co-pulverized (rotation: 60 rpm, 40 minutes). To the resulting co-pulverized powders were added 56.5 g of anhydrous lactose, 24.25 g of partly pregelatinized starch, 5 g of HPC and 23.25 g of carmellose. The resulting mixture was then subjected to wet granulation followed by size reduction. After mixing further with 1 g of magnesium stearate, the resulting mixture was compression-molded with a tabletting machine to give tablets of the present invention having components as mentioned below, each tablet weighing 235 mg in total.

	<u>Tablet formulation</u>	<u>Components (mg)</u>
	Flutamide	62.5
	Crystalline cellulose	56.25
	SDS	6.25
5	Anhydrous lactose	56.5
	Partly pregelatinized starch	24.25
	HPC	5
	Carmellose	23.25
	Magnesium stearate	1

10

Example 7

1.9 g of SDS was milled in a ball mill (rotation: 60 rpm, 5 minutes). To the milled SDS were added 37.1 g of crystalline cellulose and 60 g of flutamide, and the resulting blend was co-pulverized (rotation: 60 rpm, 40 minutes). To the resulting co-pulverized powders were added 28.1 g of anhydrous lactose, 38.2 g of corn starch and 5 g of partly pregelatinized starch. The resulting mixture was subjected to wet granulation followed by size reduction. After mixing further with 0.7 g of magnesium stearate, the resulting mixture was compression-molded with a tabletting machine to give tablets of the present invention having components as mentioned below, each tablet weighing 171 mg in total.

	<u>Tablet formulation</u>	<u>Components (mg)</u>
	Flutamide	60
	Crystalline cellulose	37.1
	SDS	1.9
5	Anhydrous lactose	28.1
	Corn starch	38.2
	Partly pregelatinized starch	5
	Magnesium stearate	0.7

10 Example 8

2 g of SDS was milled in a ball mill (rotation: 60 rpm, 5 minutes). To the milled SDS were added 48 g of crystalline cellulose and 60 g of flutamide, and the resulting blend was co-pulverized (rotation: 60 rpm, 40 minutes). To the resulting co-pulverized powders were added 28 g of anhydrous lactose, 13 g of partly pregelatinized starch, 3 g of HPC and 20 g of carmellose. The resulting mixture was then subjected to wet granulation followed by size reduction.

15 After mixing further with 1 g of magnesium stearate, the resulting mixture was compression-molded with a tabletting machine to give tablets of the present invention having components as mentioned below, each tablet weighing 175 mg in total.

20

	<u>Tablet formulation</u>	<u>Components (mg)</u>
	Flutamide	60
	Crystalline cellulose	48
	SDS	2
5	Anhydrous lactose	28
	Partly pregelatinized starch	13
	HPC	3
	Carmellose	20
	Magnesium stearate	1
10		

Example 9

1.8 g of SDS was milled in a ball mill (rotation: 60 rpm, 5 minutes). To the milled SDS were added 48 g of mannitol and 60 g of flutamide, and the 15 resulting blend was co-pulverized (rotation: 60 rpm, 40 minutes). To the resulting co-pulverized powders were added 56.65 g of anhydrous lactose, 24.3 g of partly pregelatinized starch, 5 g of HPC and 23.25 g of carmellose. The resulting mixture was then subjected 20 to wet granulation followed by size reduction. After mixing further with 1 g of magnesium stearate, the resulting mixture was compression molded with a tabletting machine to give tablets of the present invention having components as mentioned below, each tablet 25 weighing 220 mg in total.

	<u>Tablet formulation</u>	<u>Components (mg)</u>
	Flutamide	60
	Mannitol	48
	SDS	1.8
5	Anhydrous lactose	56.65
	Partly pregelatinized starch	24.3
	HPC	5
	Carmellose	23.25
	Magnesium stearate	1
10		

Example 10

62.5 g of flutamide, 92 g of anhydrous lactose, 20 g of polyethylene glycol 4000, 20 g of SDS and 140 g of croscarmellose sodium were mixed with each other, and the resulting mixture was subjected to a heat treatment at 65°C for 15 minutes for thermal granulation. After size reduction, 0.5 g of magnesium stearate was added to the granulated product, the resulting blend was compression-molded with a tabletting machine to give tablets of the present invention having components as mentioned below, each tablet weighing 235 mg in total.

	<u>Tablet formulation</u>	<u>Components (mg)</u>
5	Flutamide	62.5
	Anhydrous lactose	92
	Polyethylene glycol 4000	20
	SDS	20
	Croscarmellose sodium	40
	Magnesium stearate	0.5

Example 11

10 20 g of SDS was milled in a ball mill
 (rotation: 60 rpm, 5 minutes). To the milled SDS was
 added 62.5 g of flutamide, and the resulting blend was
 co-pulverized (rotation: 60 rpm, 40 minutes). To the
 resulting co-pulverized powders were added 92 g of
 15 anhydrous lactose, 20 g of polyethylene glycol 4000 and
 40 g of croscarmellose sodium. The resulting mixture
 was subjected to a heat treatment at 65°C for 15 minutes
 for thermal granulation. After size reduction, 0.5 g of
 magnesium stearate was added to the resulting powders.
 20 The resulting blend was compression-molded with a
 tableting machine to give tablets of the present
 invention having components as mentioned below, each
 tablet weighing 235 mg in total.

	<u>Tablet formulation</u>	<u>Components (mg)</u>
	Flutamide	62.5
	Anhydrous lactose	92
	Polyethylene glycol 4000	20
5	SDS	20
	Croscarmellose sodium	40
	Magnesium stearate	0.5

Example 12

10 25 g of SDS was milled in a ball mill
(rotation: 60 rpm, 5 minutes). To the milled SDS was
added 125 g of flutamide, and the resulting blend was
co-pulverized (rotation: 60 rpm, 40 minutes). To the
resulting co-pulverized powders were added 285.3 g of a
15 lactose hydrate/crystalline cellulose physical mixture
(Microcelac, Meggle GMBH, Wasserburg), 20 g of
polyethylene glycol 4000 and 10 g of croscarmellose
sodium. The resulting mixture was subjected to a heat
treatment at 65°C for 15 minutes for thermal
20 granulation. After size reduction, 2.35 g of light
anhydrous silicic acid and 2.35 g of magnesium stearate
were added to the powders, the resulting blend was
compression-molded with a tabletting machine to give
tablets of the present invention having components as
25 mentioned below, each tablet weighing 235 mg in total.

	<u>Tablet formulation</u>	<u>Components (mg)</u>
	Flutamide	62.5
	MICROCELAC	142.65
	Polyethylene glycol 4000	10
5	SDS	12.5
	Croscarmellose sodium	5
	Light anhydrous silicic acid	1.175
	Magnesium stearate	1.175

10 Next, the dissolution tests and the animal tests for the flutamide preparations of the present invention as obtained in the Examples as stated above, and the results from those tests are described below, as compared to a conventional preparation.

15 Test 1:

Dissolution test

1. Specimen

Control: Odyne Tablet (flutamide content: 125 mg,
Nihon Kayaku K.K.)

20 Present invention: Tablet of Example 1

2. Method

Using the two specimens as identified above, Dissolution Test 2 (a paddle method) was performed, respectively, according to the following the procedures

as defined in the Japanese Pharmacopoeia, 13th revision. The conditions are set forth in detail hereinabove. The paddle was rotated at 50 rpm, and 900 ml of 1% SDS aqueous solution was employed as a test solution. The 5 dissolution rate was calculated from the amount of flutamide dissolved out, according to the following equation.

Dissolution rate (%)
= (amount of flutamide dissolved out)/(amount of
10 flutamide originally contained in a specimen) x 100

3. Results

The results are shown in Fig. 1. As is evident from Fig. 1, the dissolution rate of the flutamide for the preparation of the present invention 15 is markedly more rapid than that of the conventional preparation.

Test 2:

Animal test

1. Specimen

20 Control: Odyne Tablet (flutamide content: 125 mg,
Nihon Kayaku K.K.)

Present invention: Tablet of Example 1

2. Method

Each of the tablets together with 50 ml of

water were orally administered into nine (9) beagles previously fasted for at least 18 hours prior to the administration. With passage of time, 5 ml each of blood was collected from beagles through the fore-limb vein. Plasma was sampled from the collected blood, and the metabolite of flutamide, i.e., 2-hydroxy-2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]propanamide (OH-flutamide), was measured by a high performance liquid chromatography.

10 3. Results

The results are shown in Fig. 2. The area under the plasma concentration-time curve (AUC), and the maximum blood level (Cmax) are also shown in Tables 1 and 2, respectively.

15 Table 1: Area under the plasma concentration-time curve (AUC)

		mean \pm SD	Maximum	Minimum
Odyne Tablet		34.96 \pm 12.24	53.48	17.45
20 Tablet of Example 1		32.26 \pm 4.0	38.22	26.23

Tablet 2: Maximum blood level (Cmax)

	mean \pm SD	Maximum	Minimum
Odyne tablet	2.63 \pm 0.7	3.61	1.43
5 Tablet of Example 1	2.54 \pm 0.23	2.98	2.25

As is well noted from the results in Tables 1 and 2, the kinesis in blood of flutamide after the 10 administration of the preparation of the present invention was substantially equivalent and comparable to that of the conventional flutamide preparation. It was also established that differences in AUC between individuals administered were less reduced in the flutamide 15 preparation of the invention than in the conventional preparation. Those results reveal that the flutamide preparation of the present invention can provide bioavailability of flutamide substantially equivalent that of Odyne tablet containing 125 mg of flutamide, 20 even though the flutamide content in the preparation of the invention is almost half of the content in Odyne Tablet. In addition, the flutamide preparation of the invention can minimize differences in bioavailability between individuals administered of flutamide.

Test 3:

Clinical trials of the flutamide preparation of the present invention

1. Specimen

5 Control: Odyne Tablet (flutamide content: 125 mg,
Nihon Kayaku K.K.)

Present invention: Tablets of Examples 1 and 2
(flutamide contents: 60 mg and
80 mg)

10 2. Method

Each of the tablets together with 100 ml of water were orally administered to nine (9) normal male adult volunteers previously fasted for at least 12 hours before administration. With passage of time, 7 ml each 15 of blood was collected from volunteers. Plasma was sampled from the blood, and the metabolite, OH-flutamide, was measured by a high performance liquid chromatography.

3. Results

20 The change in the level of the metabolite in plasma is shown in Fig. 3. The obtained AUC and Cmax are also shown in Table 3.

Table 3

	Area under the plasma concentration-time curve concentration (AUC)	Maximum blood (Cmax)
Odyne tablet	1705.5 ± 625.4	300.3 ± 104.6
Tablet of Example 1 (60 mg)	1400.9 ± 357.9	305.5 ± 58.8
Tablet of Example 2 (80 mg)	1932.8 ± 483.0	396.2 ± 113.0

The results in Table 3 reveal that the blood kinesis of flutamide after the administration of the preparation of the invention was substantially comparable to that of the control group. It was thus established that the flutamide preparation of the present invention exhibits the bioavailability of flutamide substantially the equivalent to or even better than that of the comparative preparation, even if the content of flutamide is reduced.

10 Industrial Applicability

The flutamide preparation of the present invention has an improved dissolution property and improved absorption of flutamide. Thus, the pharmaceutical preparation of the invention can provide a higher bioavailability with a less flutamide content.

CLAIMS

1. A pharmaceutical solid preparation comprising flutamide as an active ingredient and having a dissolution property that, when determined according to a paddle method, at least 50% of the flutamide dissolves out from the preparation 30 minutes after initiation of a test according to the paddle method.
2. The pharmaceutical solid preparation according to claim 1, wherein at least 75% of the flutamide dissolves out from the preparation.
3. The pharmaceutical solid preparation according to claim 1, wherein at least 85% of the flutamide dissolves out from the preparation.
4. The pharmaceutical solid preparation according to any one of claims 1 to 3, comprising flutamide as an active ingredient together with a pharmaceutically acceptable additive.
5. The pharmaceutical solid preparation according to claim 4, wherein said pharmaceutically acceptable additive is crystalline cellulose.
6. The pharmaceutical solid preparation according to any one of claims 1 to 5, wherein flutamide is contained in the preparation in the range of 30 to 200 mg per unit dosage form.
- 25 7. The pharmaceutical solid preparation according to any one of claims 1 to 5, wherein flutamide is in the range of 50 to 90 mg per unit dosage form.

8. The pharmaceutical solid preparation according to any one of claims 1 to 7, which is in the form of a tablet.
9. The pharmaceutical solid preparation according to claim 4, which comprises flutamide of 20 to 40 wt% based on the total weight of the preparation and the balance of pharmaceutically acceptable additives.
10. The pharmaceutical solid preparation according to claim 1, which is obtainable by formulating a co-pulverized mixture of flutamide with an excipient and/or a solubilizer into a pharmaceutical solid preparation.
11. The pharmaceutical solid preparation according to claim 10, wherein at least 90% of the co-pulverized mixture passes through a sieve of 48 mesh, as determined according to a powder size distribution test for a powdery preparation.
12. The pharmaceutical solid preparation according to claim 10, wherein said co-pulverized mixture and said solubilizer are contained in the range of 0.3 to 2.0 parts by weight and 0.005 to 0.5 part by weight, respectively, per part by weight of flutamide.
13. The pharmaceutical solid preparation according to any one of claims 1 to 12, wherein said excipient is crystalline cellulose, and said solubilizer is sodium lauryl sulfate.
14. A method for manufacturing a flutamide pharmaceutical preparation which comprises the steps of: subjecting flutamide and an excipient and/or a

solubilizer to co-pulverization using a communiting machine; and

formulating the co-pulverized mixture into a pharmaceutical solid preparation.

5 15. The method according to claim 14, wherein said co-pulverization is carried out using a ball mill.

16. The method according to claim 14, wherein said co-pulverization is carried out using a surface modifying machine.

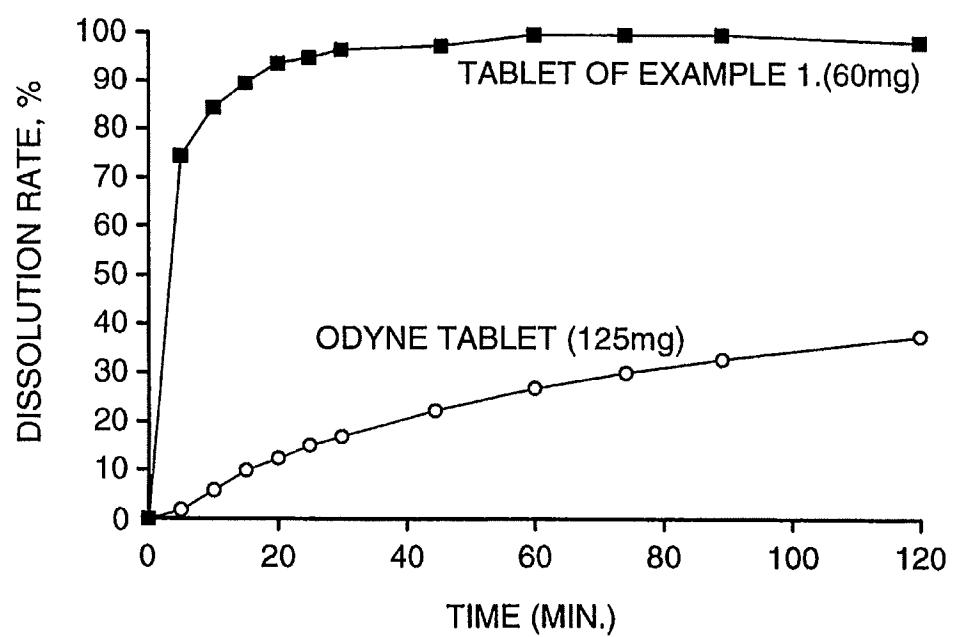
10 17. The method according to claim 14, wherein said solubilizer has been previously milled using a ball mill, then to the resulting milled powders are added flutamide and the excipient, followed by co-pulverization by a communiting machine and formulation 15 into a pharmaceutical solid preparation.

18. The method according to claim 14, wherein flutamide, the excipient and the solubilizer have been mixed with each other, then the resulting mixture is subjected to co-pulverization by a surface modifying 20 machine followed by formulation into a pharmaceutical solid preparation.

19. The method according to any one of claims 14 to 18, wherein said excipient is crystalline cellulose, and said solubilizer is sodium lauryl sulfate.

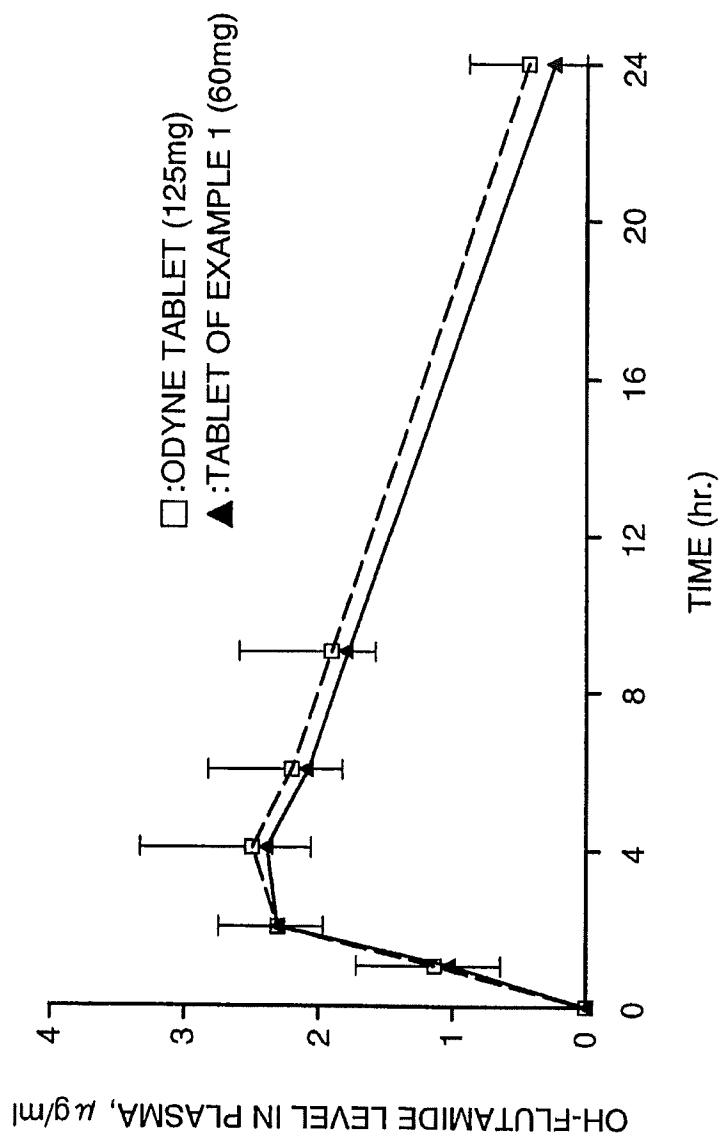
1 / 3

FIG.1



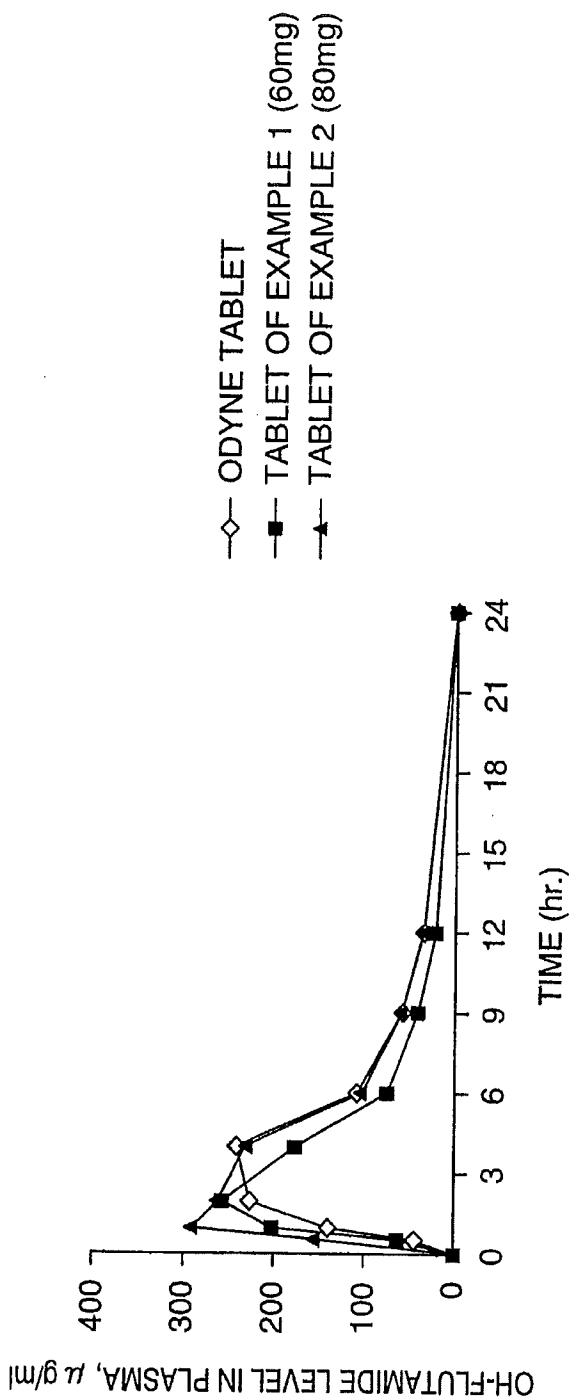
2 / 3

FIG.2



3 / 3

FIG.3



INTERNATIONAL SEARCH REPORT

Inte	lational Application No
PCT/JP 98/01769	

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61K31/165 A61K9/14 A61K9/20

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 97 02815 A (NIPPON KAYAKU KK ;AOKI MINORU (JP); SHOUJI EITOSHI (JP); YAZAWA YU) 30 January 1997 see abstract see page 14, line 17 - page 15, line 20</p> <p>-----</p> <p>ADEL M S ET AL: "IN VITRO EVALUATION OF FLUTAMIDE-CARRIER SYSTEMS. PART 2: Preparation and evaluation of flutamide systems with alpha-cyclodextrin and beta-cyclodextrin" PHARMAZIE, vol. 52, no. 6, June 1997, pages 470-472, XP000691086 see abstract see figure 4 see page 472, column 2, paragraph 3.2.5</p> <p>-----</p> <p style="text-align: right;">-/--</p>	1,2,4,6, 9
P, X		1,2,4

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the International search report
18 June 1998	02/07/1998
Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patenlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	La Gaetana, R

INTERNATIONAL SEARCH REPORT

Inte	rnational Application No
PCT/JP 98/01769	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	<p>ADEL M S ET AL: "IN VITRO EVALUATION OF FLUTAMIDE-CARRIER SYSTEMS. PART 1: Preparation and evaluation of flutamide systems with polyvinyl pyrrolidone and polyethylene glycol 4000 and 6000" PHARMAZIE, vol. 52, no. 5, May 1997, pages 373-375, XP002067871</p> <p>see abstract see figure 3 see page 375, column 2, paragraph 3.2.5</p> <p>---</p>	1,2
A	<p>US 4 474 813 A (NERI RUDOLPH O ET AL) 2 October 1984</p> <p>cited in the application</p> <p>see abstract see column 1, line 67 - column 2, line 2 see column 2, line 14-20 see column 2, line 25-35 see claims 1,3</p> <p>---</p>	1,4-6,8, 9,13
A	<p>EP 0 543 541 A (SCHERING CORP) 26 May 1993</p> <p>see abstract see page 2, line 48-51 see page 3, line 18-43 see examples see claims 8,9</p> <p>---</p>	1-6,8,13
A	<p>EP 0 577 215 A (STERLING WINTHROP INC) 5 January 1994</p> <p>see abstract see page 3, line 17 see page 3, line 35-44 see page 3, line 54 see page 4, line 44-58 see page 5, column 29-31</p> <p>-----</p>	10,14-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 98/01769

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9702815	A	30-01-1997	JP	9077663 A	25-03-1997
US 4474813	A	02-10-1984	NONE		
EP 0543541	A	26-05-1993	US	5162117 A	10-11-1992
			AU	3057492 A	15-06-1993
			WO	9309771 A	27-05-1993
EP 0577215	A	05-01-1994	US	5399363 A	21-03-1995
			AU	675432 B	06-02-1997
			AU	4156093 A	06-01-1994
			CA	2098242 A	02-01-1994
			CN	1084391 A	30-03-1994
			CZ	9301316 A	16-02-1994
			FI	933040 A	02-01-1994
			HU	64832 A	28-03-1994
			JP	7165562 A	27-06-1995
			MX	9303950 A	31-01-1994
			NO	932403 A	03-01-1994
			NZ	248042 A	26-10-1994
			SK	68193 A	02-02-1994
			US	5494683 A	27-02-1996